30 Years on: How the Neurodevelopmental Hypothesis of Schizophrenia Morphed Into the Developmental Risk Factor Model of Psychosis

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Abstract

At its re-birth 30 years ago, the neurodevelopment hypothesis of schizophrenia focussed on aberrant genes and early neural hazards, but then it grew to include ideas concerning aberrant synaptic pruning in adolescence. The hypothesis had its own stormy development and it endured some difficult teenage years when a resurgence of interest in neurodegeneration threatened its survival. In early adult life, it over-reached itself with some reductionists claiming that schizophrenia was simply a neurodevelopmental disease. However, by age 30, the hypothesis has matured sufficiently to incorporated childhood and adult adversity, urban living and migration, as well as heavy cannabis use, as important risk factors. Thus, it morphed into the developmental risk factor model of psychosis and integrated new evidence concerning dysregulated striatal dopamine as the final step on the pathway linking risk factors to psychotic symptoms.

Key words: neurodevelopment; sociodevelopment; dopamine; risk factors

The Origins of the Neurodevelopmental Hypothesis

A neurodevelopmental approach to psychosis was first postulated by the Scottish psychiatrist Thomas Clouston in 1891.[1] However, his ideas were soon displaced by Kraepelin's conceptualization of dementia praecox as an adult onset neurodegenerative disorder,[2] a view which held sway for nearly a century. Indeed, in the late 1970s, when Johnstone et al[3,4] demonstrated that people with chronic schizophrenia had lateral ventricular enlargement and cognitive deficits, they interpreted their findings as confirming "the dementia of dementia praecox."

However, in 1982, we reported that monozygotic (MZ) twins with schizophrenia had larger cerebral ventricles than their MZ but well cotwins. This implied that the larger ventricles were environmental in origin, and we noted that the affected twins had been exposed to more severe perinatal hazards.[5] In a series of articles, we con- firmed the role of pre- and perinatal complications in a larger number of discordant as opposed to concordant MZ twins[6] as well as in singleton patients with schizophrenia[7]; the latter had, of course, been previously reported, particularly from Scandinavia.[8] However, now we could link the neuroimaging findings with the emerging paediatric literature showing that periventricular bleeding in the brains of neonates exposed to prematurity and/or hypoxia often resulted in ventricular enlargement.[7,9] We also pointed to the evidence that people with schizophrenia were more likely to have been born in the late winter and spring, possibly due to prenatal exposure to maternal infections.[9]

These facts, and what we termed the "curious epiphemenomena" of schizophrenia[10] such as childhood neuromotor and minor physical anomalies, could not readily be accommodated within the Kraepelinian degenerative model. As Jablensky et al[11] have demonstrated elsewhere in this issue, interest in a developmental approach had already begun to revive, and so the neurodevelopmental hypothesis was explicitly proposed by Weinberger[12] in the United States and by ourselves[8] in the United Kingdom. Subsequent studies confirmed that low birth- weight,

hypoxia, and other obstetric hazards[7,13] are linked to increased risk of schizophrenia, as are prenatal exposure to viral infection[14] and nutritional deficiencies.[15] Some studies reported that obstetric events were associated with brain structural abnormalities in schizophrenic patients,[16] but others did not. This latter was surprising since the sequelae of hypoxia and other fetal hazards can readily be seen in the brains of nonpsychotic adults who had been born very preterm.[17] In retrospect, it seems that the developmental changes are masked in people with schizophrenia by the effects of antipsychotics and lifestyle factors such as illicit drug abuse on the brain.[18] As exception is abnormal gyrification which remains a marker of aberrant foetal development in schizophrenia and is associated with lack of treatment response.[19]

Evolution has, of course, provided the brain with resilience to insult. For example, Marin[20] points out that during childbirth, a reduction in the intracellular chloride concentration of neurons leads to an excitatory-to-inhibitory switch of γ-amino butyric acid actions which increases the resistance of neurons to hypoxic damage during delivery. Thus, an important question is whether part of the genetic predisposition to schizophrenia may operate by impairing the resilience of the fetal and neo- natal brain.[21] Furthermore, early insults to the brain can result in the developing neuronal circuits reorganizing well into adulthood. Thus, the pathological neural connectivity in some adults with schizophrenia may be the result of multiple compensatory mechanisms operating throughout development. Certainly, such is the case for adults who were born preterm.[17,22]

An important component of early formulations of the neurodevelopmental hypotheses was neuropathological report of hippocampal aberrations that could have only arisen through abnormal early neuronal migration.[23] Unfortunately, these reports were never replicated and gradually faded from view. However, support for the neurodevelopmental hypothesis came from rodent models such as the neonatal ventral hippocampal lesion model[24] and prenatal exposure to methylazoxymethanol acetate (MAM).[25] The adult offspring of MAM-treated rats displays many characteristics found in schizophrenia, including neuroanatomic changes (thinning of limbic cortices with an

increase in cell packing density, loss of parvalbumin interneurons), behavioral deficits (prepulse inhibition, latent inhibition), and increased locomotion in response to amphetamine.[25] Such animal models are described in detail by Kanyuch and Anderson elsewhere in this issue[26]

The neurodevelopmental hypothesis marched on, fuelled by cohort studies which examined characteristics of preschizophrenic children. Thus, an initial analysis of the British 1946 Birth Cohort by Jones et al[27] showed subtle neuromotor and speech delays, solitariness, and lower educational test scores by age 8. Then, using data from the Dunedin Longitudinal Study, our group reported that minor psychotic symptoms in early adolescence predicted increased risk of adult psychosis[28] and showed how children destined to develop schizophrenia-like psychoses gradually fell increasingly behind normal children in cognitive capacities as they aged from infancy to adolescence[29]

Part of the success of the neurodevelopmental hypothesis can be attributed to its elasticity. For example, early papers postulated that the effects of genetic predisposition[30] and early adverse events[7] would only manifest as psychosis in early adulthood when normative maturational changes unmasked the earlier insult. However, in 1994, Keshavan[31] relaunched the hypothesis originally proposed by Feinberg[32] that the critical process might be aberrant synaptic pruning during adolescence. Support for this latter view has recently come from Sekar et al[33] who claim that variation in compliment C4 genes may induce excessive synaptic pruning and from evidence that cortical volume loss appears to occur as psychosis onsets in adolescence and early adult life.[34]

The Model Expands to Include Social and Drug Exposures

Thus, neurodevelopmental models began to allow for disruptions to normal neural development throughout fetal life, childhood, and adolescence. This revision opened the door for consideration of the influence of other environmental exposures. A systematic review by McGrath et al[35] convinced most researchers that there was considerable variation in the incidence of schizophrenia across populations. This had important aetiological implications—findings of variation in

incidence were used to argue for more environmental and contextual influences on schizophrenia risk. Urban birth and upbringing, and indeed degree of urbanicity, were found to be associated with later risk of schizophrenia,[36] and so, risk for schizophrenia was connected to area-level, rather than to purely individual-level, variables.[37] Of course, urbanicity must be a proxy for some other causal factor—crime, social fragmentation, and isolation have all been proposed.[37,38]

Schizophrenia incidence was found to be increased in most migrant populations but especially in black people who had migrated into predominantly white European countries[39], interestingly, living in areas where there is a substantial population of similar immigrants ameliorates the risk.[40] A range of adversities in childhood such as loss of a parent, maltreatment, physical and sexual abuse, and bullying were also associated with increased risk,[38] as were more proximal adverse life events.[41] Now real-time sampling techniques have shown that patients with schizophrenia have greater sensitivity to everyday hassles than do controls and have linked even mild stress to increases in psychotic symptoms.[42] Such findings extended the neurodevelopmental model and led to the proposal of a parallel sociodevelopmental model.[43]

Increasing attention was also paid to drug-induced psychosis[44] and in particular to the role of cannabis. In spite of residual scepticism,[45] now the consensus is that heavy use of cannabis, especially of high-potency and synthetic forms, has a consistent, dose-related, effect in increasing risk of both psychotic symptoms and schizophrenia-like psychoses.[46,47]

All Roads Lead to Dopamine

Interest turned mechanisms underlying the onset of psychosis, and in particular the role of dopamine as the final common pathway underlying schizophrenia,[48] and more recently, manic psychosis.[49] Increased dopamine synthesis capacity in the associative striatum is characteristic of people with psychotic disorders: furthermore, it is already detectable at the onset of prodromal symptoms and increases with proximity to transition into frank psychosis.[50,51]

In rodents, acute stressors result in increased synthesis and release of striatal dopamine as dose isolation rearing as well as exposure to

inflammatory challenges in utero.[51] Similarly, position in the social hierarchy affects the dopamine system in monkeys.[51]

As Kanyuch and Anderson point out elsewhere in this issue,[26] early developmental disruption makes the dopamine system hyper-responsiveness to stress, particularly during the rodent equivalence of adolescence.[52] Emerging evidence shows similar effects in humans. For example, young adults who were exposed to childhood abuse or who are migrants show increased striatal dopamine synthesis capacity and increased dopamine release to experimentally induced psychosocial stress.[53,54]

In general, risk factors for psychosis seem to be associated with increased striatal dopamine. However, two exceptions have been noted so far. Thus, our follow-up into adult life of infants who were born very preterm with perinatal brain injury show reduced dopamine synthesis capacity compared to those born very preterm without perinatal brain injury and controls born at full term; hippocampal volume was positively correlated with striatal dopamine synthesis capacity but was reduced in the peri- natal brain injury group.[55] Similarly, chronic cannabis users, like other drug abusers, have low striatal dopamine, leading to the idea that in such individuals the locus of susceptibility may not be presynaptic but rather due to postsynaptic supersensitivity.[56]

Genetics

In contrast to 1987, we now know that schizophrenia risk is largely mediated by numerous common genetic variants each of tiny effect,[57] with a small proportion resulting from copy number variants with larger effect size. Some of these latter are shared with autism and learning disability, suggesting to Owen et al[58] that there exists a neurodevelopmental continuum of genetic risk.

It is now possible to derive a polygenic risk score for schizophrenia (PRS-SCZ) which reflects polygenic loading for the illness.[57] The PRS-SCZ accounts for about 9% of variance in caseness in studies of psychotic patients and controls.[59] Interestingly, it has been associated with neurodevelopmental problems and/or negative symptoms in several studies of non-ill children,[60] adolescents,[61] and adults.[62] In the

huge UK Biobank sample, the PRS- SCZ predicts lower performance on a variety of cognitive tests.[63] Schizophrenia patients with intellectual disability are particularly likely to show enrichment of rare damaging variants in developmental disorder genes, but a weaker but significant enrichment exists through- out the larger schizophrenia population.[64] Thus, many of the genetic variants associated with schizophrenia impact on brain development and in particular in cognitive development,[65] thus confirming an early article[27] entitled "The Genetics of Schizophrenia is the Genetics of Neurodevelopment."

Genome-Wide Association studies have not implicated genes directly involved in dopamine synthesis or release but instead point to upstream and downstream pathways linked to dopamine. Thus, a number of schizophrenia risk genes converge on glutamatergic systems which, of course, influence dopamine synthesis and release[66] In addition, other risk genes affect dopamine receptors (eg, DRD2) and postsynaptic signal transduction pathways (AKT1 and 3) and thus modulate postsynaptic dopaminergic neurotransmission; DRD2 and AKT1 appear to influence vulnerability to cannabis-associated psychosis.[67] Thus, risk genes for schizophrenia may play two disruptive roles: those influencing upstream factors render the midbrain dopamine neurons more vulnerable to dysregulation by the sociodevelopmental risk factors discussed earlier, while those influencing downstream factors amplify the effects of dysregulation.[66]

The Developmental Risk Factor Model

By the early years of the 21st century, the neurodevelopmental hypothesis was widely accepted. However, two threats to its viability appeared. First, interest in neurodegeneration began to revive following the demonstration that over the course of schizophrenia, the brain changes appeared to worsen[68,69] Some researchers returned to neo-Kraepelinian notions of progressive brain changes due to some intrinsic schizophrenic process.[68,69] However, it was subsequently shown that the changes were due to a combination of the effects of antipsychotics, illicit drug use, and the unhealthy life- style of people with schizophrenia.[17,70]

At the other extreme, another threat to the plausibility of the hypothesis arose from the uncritical adoption of the reductionist view that schizophrenia is simply a neurodevelopmental disorder.[71] It is obvious that this is not so, at least not in the way that autism or learning disability are neurodevelopmental disorders; rather neurodevelopmental risk factors interact with adverse social and drug risk factors, most of which act during development. Thus, deficits in neuro- and social-cognition, secondary to subtle abnormalities in neural networks, set some children on a trajectory of increasing scholastic difficulties, asociality, and isolation, features which are often rebadged in later life as primary negative symptoms. A cascade of increasing deviance occurs, and finally drug abuse, or exposure to victimisation or other adverse life events results in dysregulated dopamine release, leading to the aberrant assignment of salience to experiences and perceptions. Exposure to repeated social adversity may also bias the cognitive schema that the child uses, to interpret these excessively salient experiences in a paranoid manner.[72] A vicious cycle can then be established: stress increases dopamine dysregulation, leading to more stress as consequence of the emerging psychotic experiences, and so further dopamine release, which eventually hardwires the psychotic interpretation.[51]

Thus, the neurodevelopmental hypothesis has gradually morphed into the Developmental Risk Factor Model,[51,66,73] an integrative framework with some similarities to Developmental Interactive Model outlined by Carpenter in Straus elsewhere in this issue.[74] Such a model has to take into account evidence which has become available and indicates that schizophrenia is not a discrete disease entity but rather the severe end of a broader multidimensional psychosis spectrum.[75] Numerous studies indicate that there exists a continuum of subclinical psychotic symptoms, often associated with subtle cognitive deficits,[76] extending into the general population and that the same factors that influence risk of schizophrenia also influence the prevalence of minor psychotic symptoms in the general population.[75–77]

Thus, liability to psychosis is distributed in the same way as liability to hypertension or obesity. If an individual's blood pressure is persistently above a certain arbitrary level (90 mmHg in many countries), they are

considered hypertensive; if the hypertension is not readily responsive to treatment, they may be further diagnosed as having severe or malignant hypertension. Similarly, if psychotic symptoms go beyond a certain threshold then a diagnosis of clinical psychotic disorder is appropriate, and if this persists and is associated with cognitive impairment of developmental origin, then a diagnosis of schizophrenia is made.

Can we intervene usefully at some point in the develop- mental cascade toward illness? For a while it was thought that prodromal or "at-risk" clinics could play an important role in preventing psychosis. However, even in those areas with well organized outreach services, only a small proportion of those who develop a first episode of psychosis comes via such clinics; only 4% in South London.[78] Consequently, if we wish to prevent a significant proportion of cases of psychosis, we must intervene at an earlier point.[79]

Initially, it seemed possible that the occurrence of minor psychotic symptoms in early adolescence might specifically predict later psychosis.[22] However, we now know that such minor symptoms indicate increased risk not only of later psychosis but also depression, suicidal ideas, and anxiety.[80] Furthermore, they do not have sufficient predictive power to be useful. One possibility worth pursuing is to target those who carry several markers of deviance. Thus, Laurens et al,[81] who examined children aged 9–12, suggested using a trilogy of antecedent markers (speech or motor delays; minor psychotic symptoms; and social, behavioural, or emotional problems) to identify those at sufficient risk to merit intervention. The Gur group[82] has shown that youth with minor psychotic symptoms show cognitive deficits, reduced executive activation, exaggerated amygdala threat responsivity, and functional network dysconnectivity. Perhaps, an algorhithm using some combination of these markers may eventually be found to have predictive value in the clinic.

There may also be a minority of cases which result from a specific remediable cause.[23,26] The Velocadiofacial Syndrome results from a deletion at 22q11.2, is associated with cognitive difficulties, and up to one-third are reported to develop psychosis. A mouse model with a homologous deletion shows deficits in working-memory and impaired

functional connectivity, accompanied by dysregulated Gsk3β signaling, which is part of the same pathway as AKT mentioned earlier.[67] Importantly, these mice can be rescued by Gsk3 antagonists,[83] holding out the hope that eventually specific interventions early in life may prevent some uncommon causes of schizophrenia.

However, such an approach is unlikely to impact on the majority of cases. Here, the knowledge that schizophrenia is the extreme of a continuum of psychosis has important implications. Preventive approaches to hypertension or obesity do not focus on identifying individuals carrying biological markers; rather they encourage members of the general population to take exercise and reduce their calory intake. A similar public health approach should be adopted to psychosis. Clearly, reducing urbanicity or migration is not within the powers of psychiatrists and minimizing childhood adversity is difficult, though not impossible. However, attempting to influence society's consumption of high-potency cannabis is an obvious approach. Estimates of the proportion of cases of first onset of psychosis which could be prevented if no one smoked cannabis have ranged from 8% to 24% in different countries.[84] Unfortunately, public policy in the USA seems to be headed in the other direction with legalisation being accompanied by increases in the consumption and potency of cannabis.[85] Is the USA sleep-walking toward higher rates of psychosis?

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